REMARKS

Applicant respectfully requests reconsideration of the application in view of the foregoing amendments and the reasons that follow.

Claim Amendments

Claim 1 is amended to recite specific embodiments, claim 5 is canceled, and new claims 12-14 are added. These amendments do not introduce any new matter. For example, the amendments to claim 1 are supported by the application as filed at page 6, paragraphs [0022] and [0023], and in original claim 6. New claims 12-14 are supported by the application as filed, for example, at page 6, paragraph [0023], and in Example 4 at pages 20-21. These amendments are made without prejudice or disclaimer, and Applicant reserves the right to pursue any canceled subject matter in one or more applications with the same rights of priority as the instant application.

Upon entry of these amendments, claims 1-4 and 6-14 will be pending. Applicant respectfully requests reconsideration of these claims.

Inventor's Declaration

The Action requires a new Inventor's Declaration setting forth the mailing address, citizenship, and residence address for the inventor's legal representative. Applicant submits herewith a Substitute Declaration with the required information.

Information Disclosure Statement

The Examiner crossed off several foreign language references from the lists of references submitted by Applicant. Applicant submits herewith an additional Information Disclosure Statement to obtain consideration of these references.

§ 103 Rejections

Claims 1-11 are rejected for alleged obviousness for the reasons set forth at pages 2-7 of the Action. Applicant respectfully traverses these rejections.

Claims 1-3, 5-8, 10 & 11

Claims 1-3, 5-8, 10 and 11 are rejected for alleged obviousness in view of Fentiman *et al.*, *Br. J. Surg.* 75: 845-46 (1988) and Pujol *et al.*, *Cancer Chemother. Pharmacol.* 36: 493-98 (1996). This combination of references, however, fails to suggest the claimed invention.

Fentiman is cited for teaching the use of tamoxifen to treat mastalgia, while Pujol is cited for teaching the percutaneous administration of 4-hydroxy tamoxifen to breast cancer patients. The Action asserts that it would have been obvious to use 4-hydroxy tamoxifen in the method of Fentiman because 4-hydroxy tamoxifen is an active metabolite of tamoxifen. This assertion overlooks the fact that 4-hydroxy tamoxifen and tamoxifen are different compounds with distinct biological properties and effects. As explained at paragraphs [0015]-[0016] of the specification, although 4-hydroxy tamoxifen is a tamoxifen metabolite, its usefulness for treating mastalgia is not presaged by previous experience with tamoxifen itself.

As further evidence on point, Applicant submits herewith a Declaration under 37 CFR § 132 by Dr. Jean Fourcroy. Dr. Fourcrouy has a Masters degree in Public Health, an M.D. and Ph.D., and is a consultant for Ascend Therapeutics, Inc., the licensee of the application.

Dr. Fourcrouy's testimony evidences that it is not possible to extrapolate from Fentiman's use of tamoxifen to the use of 4-hydroxy tamoxifen described in the application, or from Pujol's administration of 4-hydroxy tamoxifen to breast cancer patients to the treatment of mastalgia. Fourcroy Declaration, ¶7. As Dr. Fourcroy explains, it is important to understand that tamoxifen and 4-hydroxy tamoxifen are distinct agents, each with unique safety and efficacy profiles. Fourcroy Declaration, ¶7. For example, tamoxifen is dependent upon cytochrome P450 enzymes for metabolism to a more active metabolite, such as 4-hydroxy-tamoxifen, and it is a potent rat liver carcinogen, unlike 4-hydroxy tamoxifen. Fourcroy Declaration, ¶8; Carthew *et al.*, *Archives of Toxicology* 75: 375-80 (2001) (already of record); Sauvez *et al.*, *Carcinogenesis* 20: 843-50 (1999) (already of record).

Each of tamoxifen and 4-hydroxy tamoxifen manifests different and unpredictable biological activities in different cells, determined in part by each compound's individual

effect on estrogen receptor conformation. As explained by Dr. Fourcroy, for both tamoxifen and 4-hydroxy tamoxifen, the final response element at the cellular level is dependent on the unique conformation of the estrogen receptor in the individual cell type. Fourcroy Declaration, ¶9; Wijayaratne *et al.*, *Endocrinology* 140: 5828-840 (1999) (submitted herewith); Giambiagi *et al.*, *J. Steroid Biochem.* 30: 213-17 (1988) (already of record). Thus, estrogen receptor binding by tamoxifen recruits different co-factors than estrogen receptor binding by 4-hydroxy tamoxifen. Fourcroy Declaration, ¶9. For example, tamoxifen initiates apoptosis in p53(-) normal human mammary epithelial cells, while 4-hydroxy tamoxifen does not. Fourcroy Declaration, ¶9; Dietze *et al.*, *J. Biological Chemistry* 276: 5384-394 (2001) (already of record). On the other hand, 4-hydroxy tamoxifen inhibits estrone sulphatase activity in mammary cancer cell lines, while tamoxifen has little effect in this regard. Fourcroy Declaration, ¶9; Chetrite *et al.*, *Anticancer Research* 13: 931-34 (1993) (already of record).

Dr. Fourcroy testifies that the state of the art, as illustrated by the publications cited above, is such that tamoxifen and 4-hydroxy tamoxifen are known to have different modes of action. Thus, according to Dr. Fourcroy, persons versed in this field understand that knowing that tamoxifen is useful in a given therapeutic regimen does not provide a reasonable basis for expecting that 4-hydroxy tamoxifen would be useful for the same purpose. Fourcroy Declaration, ¶10.

Dr. Fourcroy also testifies that the present invention provides significant advantages over the state of the art, particularly over the use of tamoxifen to treat mastalgia. Fourcroy Declaration, ¶10. This is because percutaneous 4-hydroxy tamoxifen offers important safety improvements for the treatment of this prevalent women's health disease. Fourcroy Declaration, ¶10. While the side effects of tamoxifen were known, it was not known that 4-hydroxy tamoxifen would be useful to treat mastalgia. Fourcroy Declaration, ¶10. Thus, the application describes a significant advance in the treatment of mastalgia. Fourcroy Declaration, ¶10.

The foregoing demonstrates that it was known in the art that tamoxifen and 4-hydroxy tamoxifen are not biologically equivalent and, therefore, are not necessarily interchangeable

for therapeutic purposes. In view of this knowledge, those skilled in the art would have had no reasonable expectation of success in using 4-hydroxy tamoxifen in place of the tamoxifen taught by Fentiman. Accordingly, the obviousness rejection is improper and should be withdrawn.

At page 3, the Action alleges that the dosages recited in the instant claims do not support their patentability because, according to MPEP 2144.05, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges." Applicant respectfully notes that this principle has no application here, where there is no teaching or suggest that any amount of percutaneously administered 4-hydroxy tamoxifen would be useful for treating mastalgia. As explained above, it is only the instant specification that suggests to use 4-hydroxy tamoxifen to treat mastalgia. Morever, Pujol reports that, at the doses of 4-hydroxy tamoxifen used in its study, percutaneously administered 4-hydroxy tamoxifen "cannot be proposed as an alternative tamoxifen treatment." Pujol, Abstract. Thus, Pujol does not even report an effective dose for the prevention of second breast cancer, let alone an effective dose for the treatment of mastalgia, as claimed.

Claim 9

Claim 9 is rejected for alleged obviousness in view of Fentiman, Pujol and Kochinke, U.S. Patent 5,613,958. This combination of references, however, fails to suggest the invention recited in claim 9, which is directed to embodiments where the 4-hydroxy tamoxifen is provided in a hydroalcoholic gel that comprises ethyl alcohol, isopropyl myristate, and hydroxypropylcellulose.

The inability of Fentiman and Pujol to teach the method recited in independent claim 1 is demonstrated above. Kochinke is cited for teaching transdermal systems that may comprise isopropyl myristate, ethanol and hydroxypropylcellulose. These teachings, however, do not remedy the inability of Fentiman and Pujol to teach the method recited in claim 1. Moreover, Kochinke is directed to a multi-layer transdermal patch, and thus has

little relevance to the hydroalcoholic gel recited in claim 9. Thus, the obviousness rejection of claim 9 is improper, and should be withdrawn.

Claim 4

Claim 4 is rejected for alleged obviousness in view of Fentiman, Pujol and Mauvais-Jarvis *et al.*, *Cancer Res.* 46: 1521-25 (1986) or Malet et al., *Cancer Res.* 48: 7193-99 (1988). This combination of references, however, fails to suggest the invention recited in claim 4, which is directed to embodiments where the 4-hydroxy tamoxifen is a *trans* isomer.

The inability of Fentiman and Pujol to teach the method recited in independent claim 1 is demonstrated above. Mauvais-Jarvis is cited for teaching that the *trans* isomer of 4-hydroxy tamoxifen is a "very active metabolite of tamoxifen," and Malet reports that both the *trans* and *cis* isomers of 4-hydroxy tamoxifen were active to inhibit breast cell division. These teachings, however, do not remedy the inability of Fentiman and Pujol to teach the method recited in claim 1. Thus, the obviousness rejection of claim 4 is improper, and should be withdrawn.

Conclusion

Applicant believes that the application is now in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this application, or should any issue remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for

such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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